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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/618,129	07/17/2000	Xiao Bing Wang	TRIM1	8510

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/618,129	WANG, XIAO BING	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *May 16, 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,8,9,11-36,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,8,9,11-36,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.00.

DETAILED ACTION

Status

1. Claims 2, 3, 8, 9, 11-36, 42 and 43 are pending.

Claims 2, 3, 8, 9, 11-36, 42 and 43 are rejected.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 2, 3, 8, 9, 11-15, 17, 23-36, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fahy et al (WO 96/30545) in view of Little et al (EP 497527).

Fahy teaches a method of claims 42 and 43 for detecting variations of a nucleotide at a defined site of a nucleic acid (see abstract) comprising:

(a) identifying a first form of a nucleic acid having a first nucleotide X at the defined site, wherein X is A, T, G, C, or U (see page 7, lines 18-37, where Fahy teaches a nucleic acid which has a particular nucleotide difference and see figure 1 for example of such a nucleic acid)

(b) performing a primer extension reaction on a nucleic acid sample containing a second nucleotide Y at the defined site using a primer extension reaction mixture (see page 7, lines 18-37 and page 8, lines 1-19) comprising,

(i) a primer that hybridizes upstream of the defined site of the nucleic acid sample so that the first unpaired base immediately downstream of the 3' end of the primer is Y (see page 7, lines 18-37 and figure 1, where the primer is immediately adjacent the divergent base),

(ii) a nucleotide combination in which nucleotides complementary to X are omitted, the nucleotide mixture combination (see page 8, lines 1-19, where Fahy teaches the use of three dNTPs and one chain terminating moiety and page 16, lines 25-37, where Fahy discusses mixture selection based upon the particular allele) consisting of:

(1) dTTP or dUTP, dCTP, and dGTP when X is T and at least one of dTTP, dCTP, dGTP or dUTP is labeled with a detectable label, or

(2) dCTP, dGTP and dATP when X is A or U and at least one of dCTP, dGTP and dATP is labeled with a detectable label, or

(3) dGTP, dATP, and dTTP or dUTP when X is G and at least one of dGTP, dATP, and dTTP or dUTP is labeled with a detectable label, or

(4) dATP, dTTP or dUTP, and dCTP when X is C and at least one of dATP, dTTP or dUTP, and dCTP is labeled with a detectable label; and

(c) analyzing the primer extension products formed in (b), wherein the presence of a labeled primer extension product results when Y and X are different nucleotides (see figure 1, for example).

(For entire invention, also see page 7, lines 18-37, page 8, especially page 8, lines 4-6, pages 13-16, especially page 16,lines 17-26, page 17, lines 1-3, pages 18-21, especially page 18, lines 1 1-14 and page 21, lines27-31, pages 60-62, for example.)

With regard to claims 2 and 3, Fahy teaches the use of DNA and RNA (see page 13, lines 21-32).

With regard to Claim 8, Fahy teaches the labeled dNTPS (non-terminator nucleotides) are labeled with the same or different detectable markers (See pages 15-16 and page 21, lines 15-23
and 27-32, for example).

With regard to claim 9, Fahy teaches the use of this invention with various labels such as radioactive or fluorescent labels (See pages 15-16 and page 21, lines 15-23, for example).

With regard to claims 11-14, Fahy teaches that the primer extension reaction can be performed by enzymatic means using template dependent enzymes (i.e., T7 DNA polymerase, Klenow fragment, reverse transcriptase, etc.) (See pages 19-20 for example).

With regard to claims 15 and 17, Fahy teaches that the primer may contain biotin (See page 21, lines 15-26, for example).

With regard to claims 23-36, Fahy teaches the source of the target nucleic acid of interest can be any form of RNA or DNA , obtained via amplification (for example), from any source such as from a human, animal, or microbe, and can comprise non-natural nucleotide analogs (See pages 9, 13-15, 17 and 58, for example).

Fahy teaches "Synthesis of the extension products is accomplished by polymerase extension of the primers until a template nucleotide is read or omitted which terminates synthesis. For example, a nucleotide in the template can be read for which no complementary dNTP is available in the extension mixture, resulting in chain termination. Or, more preferably, a nucleotide can be read for which a complementary chain terminating base pairing entity is available, likewise resulting in chain termination (see page 19, lines 8-17)." While this express teaching suggests that extension need not occur at all, meeting the limitations of the claims, it is not clear if Fahy contemplated detection when no primer extension product was formed due to no addition.

Little expressly teaches, in an extension method with only 1, 2 or 3 nucleoside triphosphates (see page 4, lines 32-48),

> "Where only 1, 2 or 3 nucleoside triphosphates are used and in use, the terminal nucleoside triphosphate of the extended diagnostic primer is only employed once, then it may be advantageous to use a dideoxy nucleoside triphosphate as the nucleoside triphosphate which in use will constitute the terminal nucleoside triphosphate of the diagnostic primer extended product. This will assist in production of a clearly terminated extension product of a diagnostic primer.
>
> If desired one or more of the nucleoside triphosphates present in the reaction mixture for the purpose of incorporation into

> the extended primer(s) may be labelled or marked in any convenient manner. Thus for example one or more of the nucleoside triphosphates may be fluorescently labelled. This labelling of the nucleoside triphosphates is of particular interest where production of an extension product of a diagnostic primer can be detected by detection of the labelled or marked nucleoside triphosphate(s) incorporated in the extension product. Where no extension product is formed no incorporation takes place and the labelled or marked nucleoside triphosphates may for example be washed away.
>
> More particularly this avoids the problem of amplification of artefactual products and thus enables good discrimination to be achieved in the presence of the labelled or marked nucleoside triphosphate(s). Where amplification is effected for example by the use of PCR any production of an artefactual product may result in amplification of that product and thus incorporation of the labelled or marked nucleoside triphosphate thereby reducing discrimination."

This teaching by Little expressly suggests that in nucleotide extension assays, where it is desired to detect an allelic variant, one alternative to extension which can be detected is the situation where no extension product is formed because no incorporation takes place. Little exemplifies such a detection in figure 15, for example, where the boxes with an X represent nonextended variants.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to follow the teaching of Fahy that "Synthesis of the extension products is accomplished by polymerase extension of the primers until a template nucleotide is read or omitted which terminates synthesis (see page 19, lines 8-11) by detecting primers where no extension product is formed as taught by Little since Little notes that such detection avoids the problem of artifacts and permits better

discrimination of the products since the unlabeled product will not interfere with the labeled product. Further, an ordinary practitioner would have been motivated to detect each possible mismatching length, including the situation where no extension occurred, since Fahy teaches that termination of extension is the point at which the reaction is completed and since Little teaches that no extension is one point of detection.

4. Claims 16 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fahy et al (WO 96/30545) in view of Little et al (EP 497527) and further in view of Soderlund (US 6,013,431).

Fahy in view of Little teach the limitations of claims 2, 3, 8, 9, 11-15, 17, 23-36, 42 and 43 as discussed above. Specifically, Fahy teaches the method of detection using a primer labeled with biotin. Fahy in view of Little do not teach the primer permits affinity separation of the primer from the unincorporated reagent and/or the nucleic acid of interest or that a solid support may be used in the separation process.

Soderlund teaches a detection method wherein the primer may contain an attachment moiety (i.e., biotin, antigens, etc.) (See col. 6, ln. 16-31, for example), that permits affinity separation of the primer from the unincorporated reagent and/or the nucleic acid of interest (col. 6, ln. 53 to col. 7, ln. 26, for example), and furthermore, that a solid support may be used in the separation process (col. 6-7, for example). Soderlund teaches using attachment moieties (which can be used for linkage to a solid support) is advantageous in aiding the detection process by determining which strand the variable nucleotide occurs (col. 6, lines 7-9), purifying the reaction to ensure only

bound material is analyzed (col. 6, lines 55-63), and making it possible to reuse the target nucleic acid if multiple determinations are to be performed on the same target sequence of interest (col. 6, lines 63-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Fahy in view of Little so as to have used a primer comprising an attachment moiety which permits affinity separation of the primer from the unincoporated reagent and/or the nucleic acid of interest and to have used a solid support in the separation process. One of ordinary skill in the art would have been motivated to modify the method of Fahy in view of Little in order to have achieved the benefit of aiding the detection process by determining which strand the variable nucleotide occurs, purifying the reaction to ensure only bound material is analyzed, and making it possible to reuse the target nucleic acid if multiple determinations are to be performed on the same target sequence of interest.

Response to Arguments

5. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

In this case, Applicant argues that the amendment to claim 42 overcomes the anticipation rejection over Fahy. This argument is persuasive and therefore the amendment necessitated the new rejection over Fahy in view of Little.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
6/16/05